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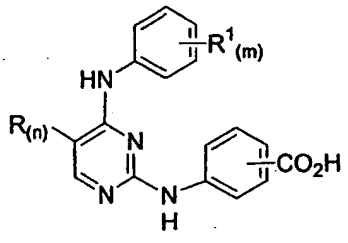
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF USING PYRIMIDINE DERIVATIVES IN THE TREATMENT OF HYPER-PROLIFERATIVE DISORDERS



(I)

(57) Abstract: A method of treating hyper-proliferative disorders comprising the administration to a patient in need thereof of an effective amount of a compound of Formula (I) wherein R is halo or CF3; n is 0 or 1; R1 is selected independently in each instance from the group consisting of halo, (C1-C3)alkoxy, and (C1-C3)alkylthiol; m is 1 or 2; or pharmaceutically acceptable salt thereof.

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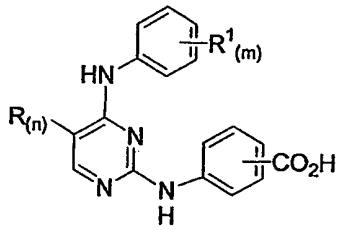
Method of Using Pyrimidine Derivatives in the Treatment of Hyper-Proliferative Disorders

Field of the Invention

This invention relates to the use of certain pyrimidine derivatives for treating hyper-proliferative disorders in mammals including humans.

Description of the Invention

This invention relates to a method of treating hyperproliferative disorders in a mammal comprising administering an effective amount of a compound of Formula I



(I)

wherein

R is halo or CF^3;

n is 0 or 1;

R^1 is selected in each instance independently from halo, $(C_1\text{-}C_3)$alkoxy, and $(C_1\text{-}C_3)$alkylthio; and

m is 1 or 2,

or a pharmaceutically acceptable salt thereof,

to a patient in need thereof.

The terms identified above have the following meaning throughout:

The term $(C_1\text{-}C_3)$alkoxy means a linear or branched saturated carbon group having from about 1 to about 3 C atoms, said carbon group being attached to an O atom. The O atom is the point of attachment of the alkoxy substituent to the phenyl ring. Such groups include but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, and the like.

The term $(C_1\text{-}C_3)$alkylthio means a linear or branched saturated carbon group having from about 1 to about 3 C atoms, said carbon group being bonded to a S atom. The S atom is the point of attachment of the alkylthio substituent to the phenyl ring. Such

groups include but are not limited to methylthio, ethylthio, *n*-propylthio, isopropylthio, and the like.

Halo includes fluoro, chloro, bromo and iodo, but is especially fluoro, bromo and chloro.

Each R^1 group can be located at the 3, 4 or 5 position on the phenyl ring. When there are two R^1 groups present in the molecule, each R^1 term shall be defined independently of the other.

The CO_2H moiety can be located at the 3, 4, or 5 position on the phenyl ring.

Illustrative examples of the compounds of Formula I that can be used in this invention include those compounds described in the specific examples below, as well as compounds that fall within Formula I that are disclosed in WO 01/64655, published July 9, 2001.

The compounds of Formula I may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration. Preferred isomers are those with the absolute configuration which produces the compound of Formula I with the more desirable biological activity. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form, and a substituent on a double bond may be present in either *Z* or *E* form.

It is intended that all isomers (including enantiomers and diastereomers), either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the scope of the present invention. The purification of said isomers and the separation of said isomeric mixtures can be accomplished by standard techniques known in the art.

The use of pharmaceutically acceptable salts of the compounds of this invention are also within the scope of this invention. The term "pharmaceutically acceptable salt" refers to either inorganic or organic acid or base salts of a compound of the present invention that have properties acceptable for the therapeutic use intended. For example, *see* S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts that are formed, for example, from

inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate. The term acid addition salts also comprises the hydrates and the solvent addition forms which the compounds of this invention are able to form. Examples of such forms are, for example, hydrates, alcoholates and the like.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides including benzyl and phenethyl bromides, and others.

Method of making the compounds used in the method of the present invention

The particular process to be utilized in the preparation of the compounds of the method of this invention depends upon the specific compound desired. Such factors as the selection of the specific R or R^1 moiety, possible at various locations on the molecule, all play a role in the path to be followed in the preparation of the specific compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

In general, the compounds used in this invention may be prepared by standard techniques known in the art and by known processes analogous thereto. The compounds of Formula I can generally be synthesized according to the methods described in WO 01/64655, published July 9, 2001, and/or by the specific examples described below.

List of Abbreviations:

t-BuOH	*tert*-Butyl alcohol
EtOAc	Ethyl Acetate
MeOH	Methyl alcohol
NaOAc	Sodium acetate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Unless otherwise stated, the term 'concentrated under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and/or (d) immersion of the plate in a cerium sulfate solution followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

Melting points (mp) were determined using an Electrothermal 9100 melting point apparatus and are uncorrected.

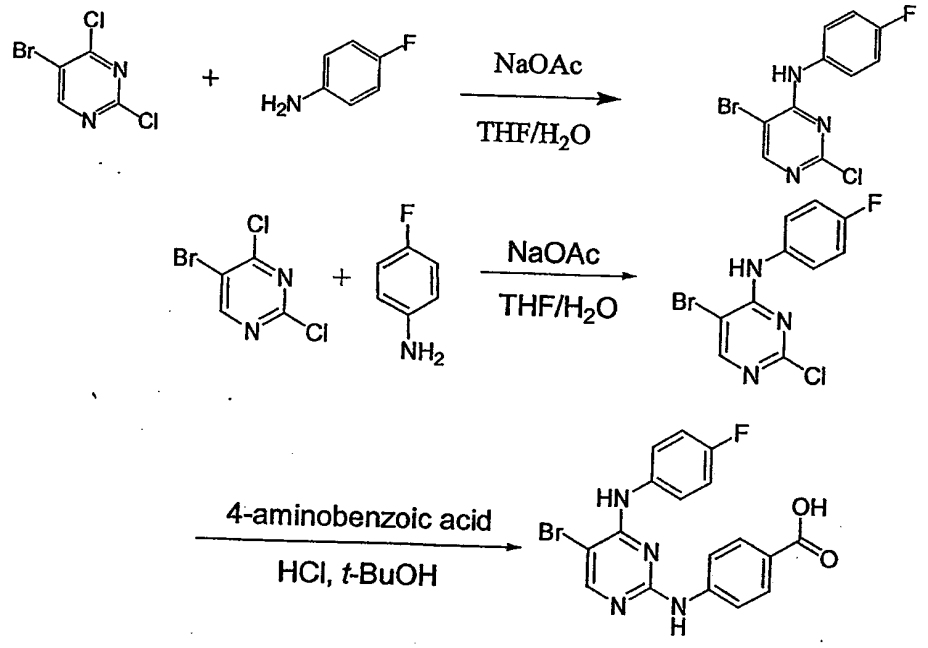
Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me_4Si (0.00) or residual protonated solvent ($CHCl_3$ 7 .26; MeOH 3.30; DMSO 2 .49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ 77 .0; d_3-MeOD; 49.0; d_6-DMSO 39.5) as standard.

HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonirile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Compound structures were consistent with analytical data (^{1}H NMR and LC-MS) for all compounds.

Example 1

Preparation of 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid



Example 1

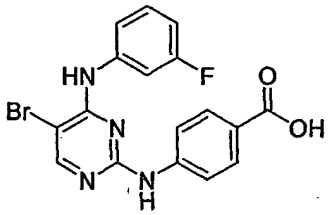
Step 1. To a solution of NaOAc (27.0 g, 330 mmol) in water (70 mL) and THF (140 mL), were added 5-bromo-2,4-dichloropyrimidine (25.0 g, 110 mmol) and 4-fluroaniline (12.2g, 110 mmol). The mixture was stirred at room temperature for 18 h then saturated $NaHCO_3$ solution (50 mL) was added and the aqueous layer was extracted with EtOAc

(150 mL x 2); the combined organic layers were dried over $MgSO_4$; filtered and concentrated under reduced pressure. The residue was treated with 200 mL hexane and filtered to give 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine as a 30.0g pale yellow powder (90%).

Step 2: To a heterogeneous mixture of 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine (12.0 g, 39.67 mmol), 4-aminobenzoic acid (5.44 g, 39.67 mmol) and *t*-BuOH (400 mL) was added HCl (12 N, 5 mL). The mixture was heated to reflux for 14 h and then allowed to cool to room temperature. The reaction mixture was reduced in volume by 80% via rotary evaporation. The resulting solid was isolated by filtration and washed with H_2O, t-BuOH and dried under reduced pressure to give 28.8 g (73%) of 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid. mp 289-290 °C; MS m/z 403 (M+); Rf = 0.1 (3/2, hexane/EtOAc).

Example 2

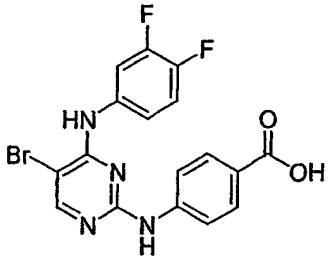
Preparation of 4-({5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate



The title compound was prepared in the same manner as Example 1 using 3-fluroaniline in place of 4-fluroaniline in step1. R_f = 0.41 (EtOAc); m.p. 284-285 °C

Example 3

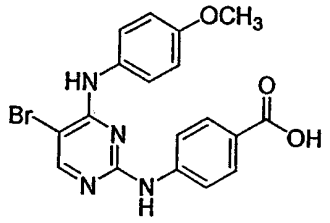
Preparation of 4-({5-bromo-4-[(3,4-difluorophenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride



The title compound was prepared in the same manner as Example 1 using 3,4-difluroaniline in place of 4-fluroaniline in step1. R_f = 0.43 (EtOAc); m.p. 299-300 °C

Example 4

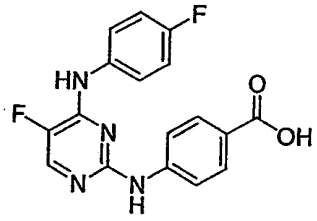
Preparation of 4-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride



The title compound was prepared in the same manner as Example 1 using 4-methoxyaniline in place of 4-fluroaniline in step1. R_f = 0.09 (1/1 EtOAc/Hexanes); m.p. 285-286 °C

Example 5

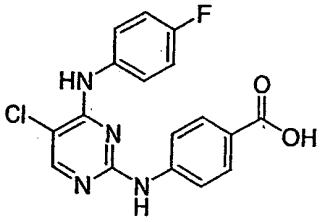
Preparation of 4-({5-fluoro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate



The title compound was prepared in the same manner as Example 1 using 5-fluoro-2,4-dichloropyrimidine in place of 5-bromo-2,4-dichloropyrimidine in step1. R_f = 0.78 (EtOAc); m.p. 254 °C

Example 6

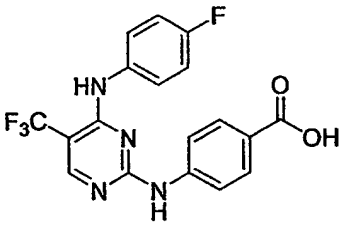
Preparation of 4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate



The title compound was prepared in the same manner as Example 1 using 5-chloro-2,4-dichloropyrimidine in place of 5-bromo-2,4-dichloropyrimidine in step1. R_f = 0.78 (EtOAc); m.p. 275 (decomposes).

Example 7

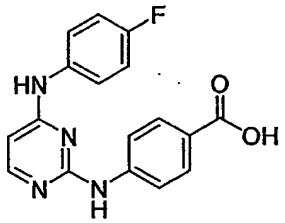
Preparation of 4-{[4-[(4-fluorophenyl)amino]-5-(trifluoromethyl)-2-pyrimidinyl]amino} benzoic acid trifluoroacetate



The title compound was prepared in the same manner as Example 1 using 5-trifluoromethyl-2,4-dichloropyrimidine in place of 5-bromo-2,4-dichloropyrimidine in step1. R_f = 0.10 (2/1 EtOAc/Hexanes); m.p. 249-252 °C

Example 8

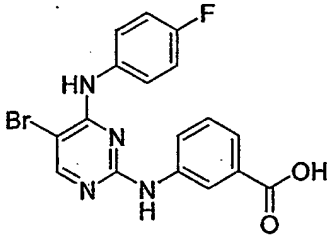
Preparation of 4-({4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid



The title compound was prepared in the same manner as Example 1 using 2,4-dichloropyrimidine in place of 5-bromo-2,4-dichloropyrimidine in step1. R_f = 0.13 (1/1 EtOAc/Hexanes); m.p. > 220 °C

Example 9

Preparation of 3-({5-bromo-4-[(4-fluoromethoxyphenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride



The title compound was prepared in the same manner as Example 1 using 3-aminobenzoic acid in place of 4-aminobenzoic acid in step 2. R_f = 0.37 (1/9/90 TFA/MeOH/CH_2Cl_2); m.p. 282-283 °C

Generally, a desired salt of a compound of this invention can be prepared in situ during the final isolation and purification of a compound by means well known in the art. Or, a desired salt can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. These methods are conventional and would be readily apparent to one skilled in the art.

Additionally, sensitive or reactive groups on the compound of Formula I may need to be protected and deprotected during any of the above methods. Protecting groups in general may be added and removed by conventional methods well known in the art (see for example, T. W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis;* Wiley: New York, (1999).

Method of treating hyper-proliferative disorders

Hyper-Proliferative Disorders

The present invention relates to a method for using the compounds described above, including salts thereof and compositions thereof, to treat mammalian hyper-proliferative disorders. Hyper-proliferative disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallblader, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

Treatment of Hper-Proliferative Disorders

The hyper-proliferative disorders known in the art and those described above have been well characterized in man, but also exist with a similar etiology in other mammals. Accordingly, mammals, including humans, can be treated by administering the compounds of Formula I and/or the pharmaceutical compositions thereof.

The method of treating hyper-proliferative disorders with the compounds of Formula I including salts thereof and compositions thereof can be illustrated by their activity in the cellular proliferation-assays described below. The following assays are two methods by which compound activity relating to treatment of the disorders identified herein can be determined.

Cellular Proliferation Assay (Plastic MTS)

Hct116 cells are seeded at a density of 3000 cells per well in 100 uL DMEM universal growth medium in 96-well culture plates and incubated overnight at 37°C in 5% CO_2 in a humidified incubator. T_0 MTS measurements are taken as described below. Cells are treated with test compounds serially diluted at 10uM, 5, 2.5, 1.25, 0.6uM, duplicate; Final concentration of DMSO in each well is 0.1% and incubated for 3 days at 37°C in 5% CO_2 in a humidified incubator. Twenty micoliters of MTS reagent (CellTiter 96 Aqueous One Solution Cell Proliferation Assay) are added to each well and plates are incubated at 37°C for 1 hour. Plates read in a Spectra MAX 250 Plate Reader at 490 nM. Percent inhibition is calculated by the following formula:

$$\% \text{ inhibition} = 1-(T_{72test}-T_0)/(T_{72ctrl}-T_0) \times 100, \text{ where}$$

$T_{72test} = OD_{490nM}$ in the presence of test compound at T = 72h
$T_{72ctrl} = OD_{490nM}$ in the absence of test compound at T = 72h
$T_0 = OD_{490nM}$ in the absence of test compound at T = 0h

In vivo assay:

Groups of female Ncr nude mice [Taconic Laboratories, NY] were inoculated with $3x10^6$ cells of HCT-116, a CRC xenograft on day 0. When tumors reached a 75 to 150 mm^3 in size (typically 6-8 days), animals were administered compounds of interest *p.o.* in a Cremaphor (12.5%; Sigma Aldrich, St. Louis, MO): Ethanol (12.5%): Saline (75%) vehicle for 14 days. The treatment volumes were 0.1mLl-test article/10g body weight. A group of 10 untreated animals was included to assess tumor response to test article vehicles. During the course of the study the animals tumor growth measurements and body weights were determined twice a week. All animals were observed for clinical signs daily and after compound administration. Tumor volume was calculated using the ellipsoid formula:

$(D \times (d^2))/2$

where,

D = diameter of the tumor at major axis

d = diameter of the tumor at minor axis

Representative compounds of Formula I demonstrated significant inhibition of cell proliferation in the assays described.

Based upon the above and other standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the

drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present inention of a pharmaceutically acceptable salt thereof can be ascertained by those skilled in the art using conventional treatment tests.

Compositions for use in the Method of this Invention

The compounds of this invention can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated.

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, otically, sublingually, rectally, vaginaly, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, cornstarch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch,

alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a

hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs

transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (See, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerin, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerin);

solvents (examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beewax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-hyper-proliferative or other indication

agents, and the like, as well as with admixtures and combinations thereof. Administration of a compound used in this invention in combination with another active agent includes simultaneous administration as well as sequential administration.

Optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone, irinotecan, raloxifen and topotecan.

The following are examples of pharmaceutical formulations that can be used in the method of the present invention. They are for illustrative purposes only, and are not to be construed as limiting the invention in any way.

Useful pharmaceutical dosage forms for administration of the compounds according to the present invention can be illustrated as follows:

Sterile Injectable Solution

A suitable amount of pure active ingredient is dissolved in sterile, injectable water to a desired concentration, for example from about 1.0 mg/ml to about 50.0 mg/ml. U.S.P. grade sodium chloride crystals (NaCl) is added to the solution such that the final concentration of NaCl is 0.9% by weight of water. The pH of the solution is adjusted to range between approximately pH 2.0 and pH 6.0 by the addition of pure (99.999%purity) hydrochloric acid. The solution is sterilized via filtration through a sterile 0.22 micron filter. The sterile solution is stored in sealed sterile vials wherein each vial contains the desired dosage unit of active ingredient per ml of injection solution.

Sterile Injectable Solution

U.S.P. grade sodium chloride (NaCl) is dissolved in sterile, injectable water to a final concentration of 0.9% NaCl by weight of water. An amount of pure (99.999% purity) hydrochloric acid is added to the NaCl solution to obtain a final pH in the range of approximately pH2.0 to pH6.0. An amount of U.S.P. grade potassium chloride crystals (KCL) is dissolved in the solution such that the final concentration of KCl is 0.1% by weight. From 0.5 part to about thirty parts by weight of active ingredient (depending on the desired end dosage unit) is added to the solution and is completely dissolved by agitation. The pH of the solution is adjusted again to between pH2.0 and pH6.0 using pure hydrochloric acid. The solution is sterilized via filtration through a sterile 0.22 micron filter and stored in sealed sterile injection vials, each containing approximately 0.5 mg to approximately 30 mg active ingredient, depending on the final dosage unit desired in the sterile injection solution.

Sterile IV Solution:

A 5 mg/ml solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over 60 minutes.

Lyophilized powder for IV administration:

The following sterile preparation can be prepared:

100 - 1000 mg of the desired compound of this invention as a lypholized powder

32- 327 mg/ml sodium citrate

300 – 3000 mg Dextran 40

The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/ml, which is further diluted with saline or dextroxe 5% to 0.2 – 0.4 mg/ml, and is administered either IV bolus or by IV infusion over 15 – 60 minutes.

Intramuscular suspension:

The following solution can be prepared:

50 mg/ml of the desired, water-insoluble compound of this invention

5 mg/ml sodium carboxymethylcellulose

4 mg/ml TWEEN 80

9 mg/ml sodium chloride

9 mg/ml benzyl alcohol

The suspension is administered intramuscularly.

Hard Shell Capsules

A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of

magnesium sterate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

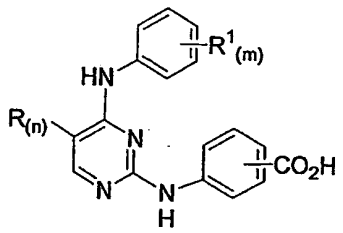
Immediate Release Tablets/Capsules

These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein. It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

What is claimed is:

1. A method of treating a hyper-proliferative disorder comprising the administration of an effective amount of a compound of Formula I



(I)

wherein

R is halo or CF^3;

n is 0 or 1;

R^1 is selected independently in each instance from the group consisting of halo, $(C_1\text{-}C_3)$alkoxy, and $(C_1\text{-}C_3)$alkylthiol;

m is 1 or 2;

or pharmaceutically acceptable salt thereof;

to a patient in need thereof.

2. A method according to claim 1 wherein R^1 is halo.
3. A method according to claim 2 wherein R is halo and n is 1.
4. A method according to claim 1 wherein the compound is selected from 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid, 4-({5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate, 4-({5-bromo-4-[(3,4-difluorophenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride, 4-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride, 4-({5-fluoro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate, and 4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate.
5. A method according to claim 1 wherein the hyper-proliferative disorder is a solid tumor disorder.
6. A method according to claim 5 wherein the solid tumor disorder is selected from colon, lung, breast, ovarian and skin cancer.
7. A method according to claim 1 wherein the hyper-proliferative disorder is breast cancer.
8. A method according to claim 1 wherein the hyper-proliferative disorder is lung cancer.

9. A method according to claim 1 wherein the hyper-proliferative disorder is colon cancer.
10. A method according to claim 6 wherein the compound is selected from 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid, 4-({5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate, 4-({5-bromo-4-[(3,4-difluorophenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride, 4-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino) benzoic acid hydrochloride, 4-({5-fluoro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate, and 4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoic acid trifluoroacetate.
11. A method according to claim 1 comprising administration of a compound of Formula I as an appropriately formulated pharmaceutical composition.